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TABLE OF CONTENTS

	<u>Page</u>
I. INTRODUCTION	1
II. REAL PARTY IN INTEREST	1
III. RELATED APPEALS	1
IV. STATUS OF CLAIMS	1
V. STATUS OF AMENDMENTS	1
VI. SUMMARY OF THE INVENTION	2
VII. ISSUES	5
VIII. GROUPING OF CLAIMS	5
IX. PROSECUTION BACKGROUND	5
X. ARGUMENT	7
A. The Enablement Rejection	7
1. Enablement Requirements	7
2. The Invention Is Enabled as Claimed	8
3. As Currently Drafted, the Pending Claims Moot the Remaining Grounds for the Examiner's Enablement Rejection	10
4. The Examiner's Burden	11
5. The Examiner's Unsupported Statements Regarding Difficulties and Complexities Associated with HIV Are Insufficient to Prove Non-Enablement	12
6. The Evidence Relied Upon by the Examiner Is Irrelevant and Outdated	14
7. The Examiner has Placed Unfair Burdens on the Appellants	16
B. The Appellants' Evidence Submitted During Prosecution Proves that the Claims Are Enabled	17
1. The Rhesus Macaque/SHIV Model Is Superior to the Chimpanzee Model	17
2. The Claimed Vaccines Effectively Protected 10 of 12 Rhesus Macaques from Infection	20
3. The Results Obtained with the Rhesus Macaque/SHIV Model Sufficiently Correlates with Results Expected in Humans	21

XI. CONCLUSION	24
CLAIMS ON APPEAL	Appendix

I. INTRODUCTION

In accordance with Rule 192(a), Appellants are filing three copies of this brief and paying a brief filing fee of \$300. Please charge any additional amount that may be due to Deposit Account No. 06-0916.

II. REAL PARTY IN INTEREST

Application Serial No. 08/909,879 on appeal is assigned to SmithKline Beecham Biologicals S.A.

III. RELATED APPEALS

An appeal in this case was filed on June 28, 1999. The Examiner reopened prosecution on the merits on September 14, 1999. A final office action was mailed on March 29, 2000. A decision to make special was granted on June 13, 2000. This second appeal follows.

IV. STATUS OF CLAIMS

Claims 19, 20, and 23-24, are pending in this application. These claims stand rejected only under 35 U.S.C. § 112, ¶ 1. There are no prior art rejections. Appellants are providing a copy of these claims in the attached appendix. The Examiner has not allowed any claims in this application.

V. STATUS OF AMENDMENTS

No amendments are made in concurrence with this brief. A Request for Reconsideration is being filed concurrently with this Brief.

VI. SUMMARY OF THE INVENTION

Appellants have discovered a novel and unobvious vaccine composition that enhances the immune response to a given antigen.¹ The inventors surprisingly found that a formulation containing an antigen with a combination of two adjuvants,² known as QS21 and 3D-MPL (3-de-O-acylated monophosphoryl lipid A), increases the body's immune response to the antigen.³ Page 1, line 18 to page 2, line 14. Previous researchers failed to teach or suggest either this particular combination or the resulting enhanced effect on the body's immunity. Claims in the parent application directed broadly to antigens in combination with QS21 and 3D-MPL have issued in U.S. Patent No. 5,750,110 to the Appellants. The present claims on appeal are directed to a vaccine comprising an HIV antigen, QS21, and 3D-MPL, and methods for enhancing the immune response to HIV by employing a vaccine of the invention.

¹ An antigen elicits an adaptive immune response and reacts specifically with corresponding antibodies or T-cell receptors, which are formed in the thymus gland. The antibody or T-cell receptor interacts with the antigen to create an immune response in a mammal. This immunity can then come into play later when the mammal has renewed contact with the antigen. The immune response lies at the heart of many well known vaccines, such as those for chicken pox, measles, polio, and hepatitis.

² An adjuvant enhances the immune response to an antigen.

³ All specification cites in this brief are to the parent application Serial No. 356,372 as found in WO 94/00153 (which issued as U.S. Patent No. 5,750,110) (Exhibit 1).

QS21 is a purified non-toxic fraction of a saponin⁴ from the bark of the South American tree *Quillaja saponaria molina*. Page 1, lines 4-16. U.S. Patent No. 5,057,540 to Kensil⁵, cited by Appellants at page 1, line 16, of the specification, discloses how to produce QS21 (identified at QA21 in Kensil), as well as other purified saponins from the *Quillaja saponaria molina* tree. Indeed, Kensil notes that 22 different saponins can be purified from this tree's bark.⁶ Of all the different saponins identified and purified from the bark of the *Quillaja saponaria molina* tree, Appellants discovered that QS21 provides an advantageous immune response in combination with 3D-MPL. Page 1, lines 18-20.

3D-MPL is a 3-deacylated monophosphory lipid A with 4, 5 or 6 acylated chains. Page 1, lines 9-12. U.S. Patent No. 4,912,094 to Myers⁷ depicts the formula of 3D-MPL at column 6. Importantly, 3D-MPL differs from MPL (monophosphoryl lipid A)—3D-MPL is the de-O-acylated product of MPL.

A vaccine containing an antigen, QS21, and 3D-MPL can be used to treat mammals suffering from or susceptible to a pathogenic infection or cancer. Page 4, line 35 to page 5, line 15. The ratio of QS21 to 3D-MPL typically falls within the range of 1:10 to 10:1, preferably 1:5 to 5:1 and often substantially 1:1. Page 5, lines 30-31. Appellants prefer the range of 2.5:1 to 1:1 of 3D-MPL to QS21. Page 5, lines 31-32.

⁴ The term "saponin" is broadly used by those skilled in the art to refer to group of plant glycosides that on shaking with water form colloidal solutions giving soapy lathers.

⁵ Exhibit 2.

⁶ See Exhibit 2, column 3, lines 17-46.

⁷ Exhibit 3.

The application specifically provides that a preferred vaccine formulation incorporates an antigen derived from HIV-1 such as gp120 or gp160. Page 4, lines 35-38. Appellants submitted empirical test data showing the efficacy of the vaccine against chimeric SHIV⁸ in rhesus macaques.⁹ The best model for studying anti-HIV vaccines is the infection of rhesus monkeys with SHIV.¹⁰ The data submitted by the Appellants show that 10 of 12 macaques vaccinated with a vaccine of the invention, and subsequently challenged with chimeric SHIV, were protected from infection at all testing points after challenge.¹¹ These results correlate with expected results in humans. As discussed below, the Appellants have met all requirements of patentability including § 112, ¶ 1 requirements. The Board should now direct the Examiner to allow the claims.

⁸ SHIV is a molecular hybrid of simian immunodeficiency virus (SIV) and human immunodeficiency virus (HIV) where the envelope protein of the SIV virus is replaced by the corresponding protein from HIV-1. The envelope protein is the principal area for protective immunity. See John Li et al., *Infection of Cynomolgus Monkeys with a Chimeric HIV-1/SIV_{mac} Virus That Expresses the HIV-1 Envelope Glycoproteins*, J. OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES 639-46 (1992) (Exhibit 4). The development of the SHIV virus is considered a significant advance in the development of an anti-HIV vaccine. See J. Stott et al., *Candidate Vaccines Protect Macaques Against Primate Immunodeficiency Viruses*, AIDS RESEARCH AND HUMAN RETROVIRUSES, 14, S-265-S-270 (Supp. 3 1998) (Exhibit 5). Presently, this is the best model for preparing an HIV vaccine.

⁹ See Voss Declaration I (Exhibit 6); Voss Declaration II (Exhibit 7).

¹⁰ See Exhibit 6, ¶ 10. See also Sanjay V. Joag, *Primate Models of Aids*, 2 MICROBES AND INFECTIONS, 223-229 (2000) (Exhibit 8).

¹¹ See Exhibit 7, ¶ 13. See also Petra Mooij et al., *A Clinically Relevant HIV-1 Subunit Vaccine Protects Rhesus Macaques From In Vivo Passaged Simian – Human Immunodeficiency Virus Infection*, 12 AIDS RESEARCH AND HUMAN RETROVIRUSES F15 (1998) (Fast Track) (Exhibit 9). Articles that are on the fast track are generally reserved for those reports that are particularly significant.

The Examiner's enablement rejection should be reversed for three reasons. First, the Examiner did not meet her burden by presenting sufficient evidence to call into question the veracity of the Appellants' specification. Second, the evidence relied upon by the Examiner in making the enablement rejection relies on an outdated and irrelevant animal model and is inappropriate for comparison with the Appellants' invention. Third, the affirmative evidence submitted by the Appellants conclusively shows that the specification meets the enablement requirement of section 112, first paragraph because that evidence establishes that the invention is efficacious in the rhesus macaque and it reasonably correlates to humans.

VII. ISSUES

The only issue presented by this appeal is whether claims 19, 20, and 23-24, are enabled under 35 U.S.C. § 112, ¶ 1.

VIII. GROUPING OF CLAIMS

For purposes of this appeal only, Appellants agree that the patentability of the pending claims, claims 19, 20, and 23-24, stands or falls together. Claim 19 reads:

A vaccine comprising:

- (a) Human Immunodeficiency Virus (HIV) antigen;
- (b) QS21; and
- (c) 3-De-O-acylated monophosphoryl lipid A (3D-MPL).

Claims 20 and 23-24 depend on claim 19.

IX. PROSECUTION BACKGROUND

The specification of the present appeal was originally filed on June 15, 1993 in what became PCT publication WO 94/00153 and was published on January 6, 1994. The application entered the national stage in the United States on February 17, 1995 and corresponding U.S. Patent No. 5,750,110 issued on May 12, 1998. The claims of the '110 patent are directed to, among other things, vaccines comprising an antigen, QS21, and 3D-MPL, and methods of treating mammals by use of the vaccine.

The application on appeal was filed on August 12, 1997, as a continuation of the application that matured into the '110 patent. The claims were directed to the use of QS21 and 3D-MPL in conjunction with either the HIV or FIV antigen.

The PTO issued the first Office Action rejecting all pending claims under 35 U.S.C. § 112, first paragraph for failing to provide an enabling disclosure. The Examiner stated that additional evidence was required to prove the efficacy of an anti-HIV vaccine. In response to the first Office Action, the Appellants provided a declaration from Dr. Gerald Voss¹² and supporting evidence demonstrating how the invention was enabled. The declaration explained how a vaccine of the invention had been tested in the murine model and had generated a strong anti-HIV humoral and CTL response. Furthermore, 2 of 4 rhesus macaques vaccinated with the claimed vaccine were protected from infection

¹² See Exhibit 6.

whereas 4 control macaques became infected.¹³ The Examiner, however, maintained the rejection in a final Office Action. The Appellants responded by canceling claims directed to FIV and the mechanism by which the invention operates. The Appellants also submitted a second declaration by Dr. Voss¹⁴ accompanied by a scientific article¹⁵ discussing the efficacy of the claimed vaccine. The second declaration described an experiment where 10 of 12 macaques vaccinated with the claimed vaccine were protected from SHIV infection while all of the non-vaccinated control macaques were infected.

In a subsequent interview with the Examiner, the Appellants explained the significance of the Voss declaration and supporting evidence and how they proved the efficacy of the pending claims. The Examiner, nonetheless, maintained the rejection in an advisory action. An appeal followed. Rather than submitting the appeal to the Board, however, the Office reopened prosecution on the grounds of obviousness-type double patenting with respect to U.S. Patent No. 5,750,110. Appellants filed a terminal disclaimer to obviate the rejections and withdrew, without prejudice or disclaimer, claims 28-31. Instead of allowing the claims, however, the Examiner issued a final rejection, based solely on the previous 35 U.S.C. § 112, ¶ 1 rejection which Appellants already addressed in the first appeal brief. Appellants' response is filed concurrently with this appeal.

¹³ See Exhibit 6, ¶ 19.

¹⁴ See Exhibit 7.

¹⁵ See Exhibit 9.

X. ARGUMENT

A. The Enablement Rejection

1. Enablement Requirement

An enabling disclosure is one that allows "those skilled in the art to make and use" the invention. *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991). This straightforward standard also requires that no "undue experimentation" be necessary to practice the invention. *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365, 42 U.S.P.Q.2d 1001, 1004 (Fed. Cir. 1997). It is perfectly proper to submit post-filing declarations or affidavits to prove that the specification, as filed, is enabling. *In re Brana*, 51 F.3d 1560, 1569 n.19, 34 U.S.P.Q.2d 1436, 1444 n.19 (Fed. Cir. 1995) (commenting that a declaration dated after the filing date "can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification.").¹⁶ When the PTO makes an enablement rejection under section 112, it bears the initial burden of explaining why it believes the claim is not adequately

¹⁶ Although the Examiner's rejection is based on non-enablement, it is closely related to utility. By determining that the Appellants' data do not correlate to human efficacy the Examiner has effectively taken the position that the invention has no utility in humans absent evidence to the contrary. Indeed, the MPEP recognizes the overlap between § 101, the utility requirement, and § 112, ¶ 1. For instance, MPEP § 2164.06(a) discusses examples of enablement in instances where information is missing and directs the reader to MPEP § 2107, General Principles Governing Utility Rejections, for a discussion of examples in the pharmaceutical arts. Therefore, case precedent directed to § 101 utility rejections is entirely appropriate and applicable here where the Examiner made a rejection because the specification purportedly lacks evidence that would convince one of ordinary skill that the invention is effective for what it claims. As in *In re Brana*, the Appellants use the articles by Joag and Mooij and the Voss declarations to address the Examiner's enablement rejection.

enabled by the invention's description. *In re Wright*, 999 F.2d 1557, 1561-62, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993).

2. The Invention Is Enabled as Claimed

The data from the Voss declarations, the Mooij article, and the review article by Joag demonstrate the efficacy of the Appellants' claimed invention at the time of filing. This evidence proves that the claims meet the enablement requirement of 35 U.S.C. § 112, ¶ 1. For instance, claims 19-23 recite vaccine compositions containing an HIV antigen, adjuvant QS21, and adjuvant 3D-MPL. Similarly, claim 24 is directed to a process for making the claimed vaccines with an HIV antigen. The disclosure teaches, at page 1, that the invention is directed to vaccines containing QS21 and 3 D-MPL. Page 1, lines 5-7. At lines 18-20, the disclosure states that formulations containing this combination "synergistically enhance immune responses to a given antigen."

By way of example, a vaccine formulation containing a malarial antigen in combination with the two adjuvants is discussed beginning on page 1, line 22. The invention is in no way limited, however, to the malarial antigen. Importantly, the disclosure teaches that "[p]referably, the vaccine formulations will contain antigen or antigenic compositions capable of eliciting an immune response against a human or animal pathogen, which antigen or antigenic composition is derived from HIV-1, (such as gp120 or gp160)" or one of several other antigens. Thus, the disclosure adequately explains how to make and use the claimed composition, and the data from Mooij should remove any doubts concerning its efficacy.

At pages 5 and 6 of the disclosure, a preferred formulation of the invention is taught and a discussion of typical human administration is also disclosed. Before turning to the examples, the disclosure summarizes the teachings by stating that "in one aspect, the invention provides a method of treatment comprising administering an effective amount of a vaccine of the present invention to the patient." Page 6, lines 25-27. Based on this disclosure and the effective protection of 10 of 12 macaques, the claims stand enabled by the specification.

3. As Currently Drafted, the Pending Claims Moot the Remaining Grounds for the Examiner's Enablement Rejection

In the first¹⁷ and second¹⁸ Office Actions, prior to the first appeal brief, the Examiner maintained rejections to the claims because they were directed to enhancing cytolytic responses, generating the production of gamma interferon, and FIV. In amending the claims after the second Office Action, the Appellants removed all reference to CTL and to γ -interferon. In other words, the mode of operation or mechanism by which the invention operates no longer appears in any of the claims. Instead, the claims now cover anti-HIV vaccines and methods of enhancing immune responses with these vaccines. Additionally, the Appellants removed language claiming FIV as an antigen.

The Appellants need not claim or even know how their invention works for "[i]t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests." *Fromson v. Advance Offset Plate, Inc.*, 720

¹⁷ Exhibit 10.

¹⁸ Exhibit 11. The two Office Actions issued by the Examiner after the first appeal brief was filed are attached as Exhibit 12 and Exhibit 13 respectively.

F.2d 1565, 1570, 219 U.S.P.Q. 1137, 1140 (Fed. Cir. 1983). The Appellants now claim what they observed: the vaccine and the enhancement of the immune response using a vaccine of the invention.

In *In re Cortright*, 165 F.3d 1353, 1360, 49 U.S.P.Q.2d 1464, 1469 (Fed. Cir. 1999), the Federal Circuit rejected an Appellant's claims directed to a method of restoring hair growth because supporting statements in the disclosure did not reflect "actual observations." In that case, Cortright claimed a method of "offsetting the effects of lower levels of a male hormone being supplied by arteries to the papilla of scalp hair follicles with the active agent 8-hydroxy-quinoline sulfate to cause hair to grow again on the scalp." *Id.* at 1355, 49 U.S.P.Q.2d at 1465. The Federal Circuit affirmed the rejection because the specification "did not disclose that anyone observed the active ingredient reach the papilla and offset the effects of lower levels of male hormones." *Id.* at 1360, 49 U.S.P.Q.2d at 1469. The Court concluded by finding that Cortright's statements "reflect[ed] no actual observations." *Id.*

Unlike in *In re Cortright*, where the Appellant had failed to provide any evidence supporting her claims, here the Appellants have presented ample evidence that their claims are enabling. That evidence includes the second declaration from Dr. Voss and an article co-authored by Dr. Voss containing *in vivo* animal data establishing the efficacy of the invention. In addition, Appellants have provided additional art that is more recent and more relevant than art used by the Examiner to maintain the enablement rejection.¹⁹

¹⁹ See *infra* Sections A.6 and B.

Thus, the Appellants have mooted the Examiner's enablement rejection by removing from examination claims directed to how the invention works.

4. The Examiner's Burden

The Examiner must accept as true the statements in the specification regarding enablement "unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *Fiers v. Revel*, 984 F.2d 1164, 1172, 25 U.S.P.Q.2d 1601, 1607 (Fed. Cir. 1993) (quoting *In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (CCPA 1971)). Thus, the Patent Office must "explain why it doubts the truth or accuracy of any statement in a supporting disclosure and . . . back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d at 224, 169 U.S.P.Q. at 370 (emphasis omitted).

The Examiner has challenged the truth of the statements made by the Appellants in the present application. The Examiner has failed, however, to support the enablement rejection. The primary evidence cited by the Examiner is from Haynes²⁰ which criticizes the use of the chimpanzee model for an anti-HIV vaccine in humans. As discussed *infra* in Section B, this criticism is irrelevant as the Appellants do not rely on that model. The fact remains that evidence submitted by the Appellants during prosecution, particularly the Voss declarations and the recent publications, proves that the specification meets the enablement requirement. Before turning to evidence submitted by the Appellants

²⁰ Barton F. Haynes, *Scientific and Social Issues of Human Immunodeficiency Virus Vaccine Development*, 260 SCIENCE 1279 (1993) (Exhibit 14).

traversing the Examiner's rejection, a careful look at the Examiner's arguments reveals that the Examiner has failed to meet her burden in presenting a *prima facie* § 112, first paragraph rejection.

5. The Examiner's Unsupported Statements Regarding Difficulties and Complexities Associated with HIV Are Insufficient to Prove Non-Enablement

The appealed claims are directed to a vaccine comprising an HIV antigen and adjuvants QS21 and 3D-MPL as well as claims for treating mammals with that vaccine. The PTO has already allowed Appellant's patent from the parent case claiming the two adjuvants in conjunction with an antigen.²¹ For example, claim 1 of the '110 patent claims a vaccine comprising "an antigen" and the same two adjuvants.

The only remaining issue is whether the Appellants are entitled to claims directed to an HIV antigen, QS21, and 3DMPL. In the first Office Action, the Examiner argues that the many obstacles documented in the literature (although no literature references are cited) prevent "one of ordinary skill in the art from accepting any vaccine or any immunization treatment or any therapeutic regimen [directed to HIV] on its face" and that "either in vivo or in vitro data, or a combination . . . must be such as to convince one of ordinary skill in the art that the proposed claims are sufficiently enabled."²² The Examiner then lists several reasons, purportedly explaining why the development of an anti-HIV vaccine would be particularly difficult. The Examiner fails, however, to specifically state why the specification is insufficient.

²¹ U.S. Patent No. 5,750,110 (Exhibit 15).

²² Exhibit 10, page 3.

To meet her burden, the Examiner must set forth sufficient reasons why the specification is not enabling, and the Examiner has simply failed to meet this burden. For example, the Examiner states that one reason HIV therapies are difficult to develop is because of the "existence of a latent form of the virus."²³ That fact does not explain, however, why the Appellants' disclosure is presumptively non-enabling. The Examiner has presented no evidence or rationale explaining why the presence of a latent form of the HIV virus is inconsistent with the claims. Indeed, claims to vaccines for antigens associated with viruses having latent forms have already issued in the parent case. For instance, it is well known that the Herpes viruses have latent forms²⁴ and the '110 patent specifically claims vaccines with two different herpes antigens. Thus, this rationale cannot be used as a basis for now rejecting an anti-HIV vaccine.

Similarly, the Examiner notes that the HIV virus is complex and diverse. That statement, does not, however, detract from the enablement of the claimed vaccine. The '110 patent claims 17 different antigens²⁵ using the very same adjuvants now before the Board on appeal. Those antigens present a diverse range of complex and genetically distinct antigens. Thus, it is inconsistent for the Examiner to rely on the genetic complexity or diversity of HIV as a basis for an enablement rejection when the very same

²³ *Id.*

²⁴ See e.g., Frank J. Jenkins & Sharon L. Turner, *Herpes Simplex Virus: A Tool for Neuroscientists*, FRONTIERS IN BIOSCIENCE 1, d241-d247 (1996) (Exhibit 16).

²⁵ These are: Herpes Simplex Virus types 1 and 2; Human Cytomegalovirus; Hepatitis A, B, C, and E; Respiratory Syncytial virus, human papilloma virus, Influenza virus, Salmonella, Neisseria, Borrelia, Chlamydia, Bordetella, Plasmodium, and Toxoplasma.

adjuvants were deemed enabled in conjunction with 17 other antigens in the parent '110 patent.

6. The Evidence Relied Upon by the Examiner Is Irrelevant and Outdated

Faced with the statements in the specification and evidence submitted in the Voss declarations proving that the claimed vaccine prevents infection of SHIV in rhesus macaques, the Examiner cites an article by Haynes from *Science* in 1993 which criticizes the chimpanzee model as a means for studying anti-HIV vaccines.²⁶ The Examiner's reliance on Haynes, however, is misplaced because the Appellants do not rely on chimpanzee data. Furthermore, the Examiner's assertion that "[t]o date the chimpanzee is the best available animal model for the study of AIDS in humans because it is the only one capable of infection with the HIV or HTLV III/LAV virus" is incorrect.²⁷ As explained *infra* in Section B, the widely accepted view among scientists today is that the rhesus macaque is the best model for studying anti-HIV vaccines—the exact model used by the Appellants to prove that the claimed vaccine has protected macaques upon challenge with chimeric SHIV. In the first Office Action, the Examiner argued that "[w]ith respect to the AIDS-associated retroviruses[,] the art does not recognize any animal model as exhibiting a direct correlation to human disease (see for example

²⁶ See Exhibit 14.

²⁷ Exhibit 14, page 4.

Haynes, *Science*, Vol. 260, 1993, page 1280 copy enclosed).²⁸ In the passage cited to by the Examiner, Haynes writes:

[N]o animal model exactly mirrors HIV infection. In general, current animal models of HIV or simian immunodeficiency virus (SIV) either do not develop AIDS symptoms, do not develop immune responses analogous to human anti-HIV T and B cell responses, or involve the use of endangered species such as chimpanzees.²⁹ (Emphasis added.)

In the second Office Action, the Examiner refers to a 1996 article by Haynes for evidence that there is no art-recognized animal model for HIV. Appellants note that the 1996 article merely cites to the 1993 article, and nothing new is added. The Examiner repeats the same arguments in the third and fourth Office Actions.

What the Examiner fails to challenge, however, is the macaque/SHIV model, the model used by Appellants as a basis for their claims. Hayes does not cite this model. The Examiner's reliance on Haynes is, therefore, outdated and can no longer be the basis for an enablement rejection. Stacked against the Examiner's antiquated evidence, the Appellants have the recent review by Joag, the Mooij article, and the in vivo evidence presented by the Voss declarations.

The Examiner unfairly gives no weight to the Voss declarations and ignores the Mooij article showing the strong correlation between the macaque/SHIV model and humans. The Examiner should not now also be allowed to ignore the recent review

²⁸ Exhibit 10, page 3.

²⁹ Exhibit 14, page 1280.

article by Joag. The data relied upon by the Appellants comes from the macaque/SHIV model, a model superior to the chimpanzee model, and the best model for studying anti-HIV vaccines today.³⁰

7. The Examiner has Placed Unfair Burdens on the Appellants

The Examiner has placed unfair and unsupported requirements on the Appellants. In the latest Office Action, the Examiner maintains that due to the "significant ongoing clinical trials" of other inventions related to HIV vaccines and because those other inventions have failed, as of yet, to be effective, "it is impossible to correlate any results in animal models of HIV infection with efficacy in humans."³¹ The Examiner's arguments and logic are gravely flawed.

The Examiner provides no verifiable evidence that such trials involve vaccines even remotely similar to Appellants' invention. It is too convenient for the Examiner, and grossly unfair to the Appellants, for the Office to rely on unauthenticated statements of purported fact as a basis for rejecting Appellants' invention. Appellants are simply unable to evaluate the reliability of the Examiner's opinion of the similarity, or lack thereof, between the vaccines used in the alleged clinical trials and the vaccines of the claimed invention.

The Office should also bear in mind that the FDA, not the Appellants, have the final say on clinical trials. Moreover, "considerations made by the FDA for approving

³⁰ See Exhibit 6, ¶¶ 10-11; Exhibit 5, page S-265.

³¹ Exhibit 13, page 3.

clinical trials are different from those made by the PTO in determining whether a claim is enabled."³² The Examiner's position is simply untenable.

B. The Appellants' Evidence Submitted During Prosecution Proves that the Claims Are Enabled

1. The Rhesus Macaque/SHIV Model Is Superior to the Chimpanzee Model

The Appellants rely on data obtained from the rhesus macaque/SHIV model to prove that the claims are sufficiently enabled to meet statutory requirements. The rhesus macaque/SHIV model was described by Mooij³³ as an effective HIV model. Furthermore, the scientific community generally agrees with Mooij that the SHIV/rhesus macaque model is an effective model. For instance, one recent paper concludes that "[m]acaque models have provided convincing evidence that vaccination against lentivirus infection is achievable."³⁴ Another article even more recently concludes that "[t]he SHIV/macaque model is a superb tool with which to address such [gp120 vaccine] issues."³⁵ By contrast, the Examiner criticizes the Appellants' application based on the chimpanzee model and gives three reasons why that model is supposedly insufficient:

³² MPEP § 2164.05

³³ Exhibit 9, pages F15, F21.

³⁴ Exhibit 5, page S-268. A lentivirus is a genus of viruses including HIV, SIV, and FIV. See DORLAND'S ILLUSTRATED MEDICAL DICTIONARY, (28th Ed.) (Exhibit 17).

³⁵ Exhibit 8, page 226. The Appellants' claims cover both the gp120 and the gp160 antigens.

1) the failure to develop symptoms of AIDS; 2) the failure to develop immune responses analogous to human responses; and 3) the endangered-species status of the common model used at the time—the chimpanzee.

In further articulating the rejection, the Examiner focused on point 1) as a key failure of the model, stating that the chimpanzee "does not develop the full-blown syndrome of AIDS, the significance of this failure being the inability to assess challenge after treatment with the purported vaccine."³⁶

The Appellants' evidence overcomes the Examiner's faulty reliance on Haynes. Dr. Voss states in his declaration that the rhesus macaque model is "one of the best animal models currently available for the investigation of potential prophylactic HIV vaccines."³⁷ Dr. Voss explains there are at least three reasons why the macaque is superior to the chimpanzee.

First, unlike the chimpanzee, the macaque is capable of getting AIDS-like symptoms from some strains of SHIV.³⁸ Researchers discovered that SIV (simian-immunodeficiency virus) causes AIDS-like symptoms in monkeys and is genetically similar to HIV-1.³⁹ However, researchers learned that the immune reactive epitopes of the SIV envelope glycoprotein differ from those in its HIV-1 counterpart. The SHIV virus overcomes this drawback by replacing the envelope protein of SIV with a human

³⁶ Exhibit 10, page 4.

³⁷ Exhibit 7, ¶ 12.

³⁸ Exhibit 6, ¶ 10.

³⁹ See Exhibit 5, pages S-265-S-266.

HIV antigen.⁴⁰ Thus, SHIV was specifically designed as a model for studying HIV infection in humans. For these reasons, the development of the SHIV model has been hailed as a "significant advance" in the study of AIDS vaccines.⁴¹

Second, infected macaques "mount a vigorous immune response similar to those observed in infected humans."⁴² Thus, there is a correlation between the macaque model and human response to the HIV virus.

Third, the macaque does not suffer from the same environmental drawback such as limited supply as the chimpanzee does. Thus, Voss Declaration I⁴³ traverses each and every criticism of animal models used by the Examiner.

Indeed, Joag supports the conclusions drawn in the Voss declarations. Joag states that due to insignificant biological differences between macaques and humans, results of gp120 vaccines using the SHIV-macaque model "can be extrapolated to humans with a high level of confidence."⁴⁴

⁴⁰ See Yichen Lu et al., *Utility of SHIV for Testing HIV-1 Vaccine Candidates in Macaques*, 12 J. OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES AND HUMAN RETROVIROLOGY 99 (1996) (Exhibit 18).

⁴¹ See Exhibit 5, page S-266.

⁴² Exhibit 6, ¶ 10.

⁴³ See *id.* at ¶ 9.

⁴⁴ Exhibit 8, page 225, Table II.

2. The Claimed Vaccines Effectively Protected 10 of 12 Rhesus Macaques from Infection

Voss Declaration II,⁴⁵ submitted to the PTO on January 25, 1999, in response to an Office Action, discusses an experiment where 12 rhesus macaques were immunized with a vaccine covered by the claims of the invention and then challenged with SHIV. The macaques were sampled numerous times after challenge and 10 of them never showed any signs of infection while all of the control macaques did. This experiment is based on research results published by Mooij et al. (Dr. Voss was an author on that paper).

In the experiment, two groups (groups A and B) of four macaques each were immunized with a vaccine of the invention containing the HIV antigen gp120_{w6 ID} which had been derived from a human AIDS patient. A third group of four macaques (group C) had previously been immunized with an inferior vaccine incorporating the same antigen. Finally, as a control, four non-immunized naive macaques were challenged.

In order to determine the efficacy of the vaccine, the authors constructed a chimeric virus (SHIV) by replacing a key viral fragment encompassing gp120 and gp41 on the SIV virus with the equivalent region cloned from the human AIDS patient. All of the macaques were challenged intravenously with the chimeric SHIV virus 4 weeks after their last immunization.

The results of the study are impressive. Ten of the twelve macaques vaccinated were protected from infection at all times after challenge. In addition, the 10 protected

⁴⁵ See Exhibit 7.

macaques showed no detectable viral burden or load. Further, the two remaining macaques "did in fact show a reduced viral burden."⁴⁶ According to Dr. Voss, "in animals which are protected from infection, there is no detectable viral burden or viral load."⁴⁷ All of the control group macaques became infected after only two weeks. Those of ordinary skill in the art would recognize that the results of these experiments prove that the claimed vaccines are enabled because they offered either complete protection or a reduced viral burden for rhesus macaques exposed to SHIV.

3. The Results Obtained with the Rhesus Macaque/SHIV Model Sufficiently Correlates with Results Expected in Humans

In the first Office Action, the Examiner required the Appellants to provide "an art-recognized animal model"⁴⁸ should the Appellants rely on animal testing data. The Examiner overstates the Appellants' burden. The MPEP directly contradicts the Examiner's position stating that evidence submitted to show the utility of an invention in the pharmaceutical arts "does not need to be in the form of an art-recognized animal model for the particular disease or disease condition to which the asserted utility relates."⁴⁹ Thus, the Examiner's requirement is in error. Nevertheless, even if an art

⁴⁶ Exhibit 7, ¶ 8.

⁴⁷ *Id.* at ¶ 6.

⁴⁸ Exhibit 10, page 3.

⁴⁹ MPEP § 2107.02.

recognized model were necessary, the rhesus macaque model is an art-recognized model due to the dramatic results achieved by the claimed invention.⁵⁰

The Appellants have presented in their responses and declarations unrefuted *in vivo* animal data that their claimed vaccines work effectively in the macaque/SHIV model—a model that is known and accepted by those skilled in the art as the best model for conducting non-human HIV-vaccine studies.⁵¹ Nevertheless, in the Examiner's Advisory Action, the Examiner maintained the rejection and found that Voss Declaration II failed to provide "convincing objective evidence that *in vitro* and animal model data reasonable correlate with *in vivo* efficacy in humans."⁵² It is first worth noting that the data in the Voss declarations is in the form of *in vivo* and not *in vitro* data. When an applicant presents evidence to overcome a rejection based on correlation of *in vitro* to *in vivo* efficacy, "the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as *reasonably* correlating to the condition."⁵³ For instance, in the second Voss declaration, the Appellants submitted proof of enablement in the form of SHIV/rhesus macaque *in vivo* data. Additionally, in the first declaration, the Appellants' submitted proof was by way of tests conducted using

⁵⁰ See Exhibit 5, page S-268.

⁵¹ See e.g., Exhibit 6, ¶¶ 10-11.

⁵² Advisory Action (Exhibit 19).

⁵³ MPEP § 2164.02 (citing *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995) (emphasis added)).

the murine model.⁵⁴ These *in vivo* data proving the efficacy of the claimed vaccine in the best animal model known today remain unrefuted.

The Examiner's arguments after the first appeal fare no better. The Examiner cites articles by Fox and Fahey for the propositions that clinical trials have been ineffective. The Examiner concludes that "since no animal model of HIV infection is known to reasonably correlate with *in vivo* efficacy in humans, Applicant's reliance on the evidence of Dr. Voss is insufficient to overcome the rejection."⁵⁵ Again, the Examiner relies on outdated scientific evidence. Fahey was published in 1992, Fox in 1994, and, as noted earlier, the newer Haynes reference was published in 1996. Furthermore, nowhere does the Examiner discuss the similarity, if any, between the Appellants' invention and the vaccines discussed by Fox and Fahey. The Examiner's reliance on Cohen (1993) and Butini (1994) is similarly misplaced.

The Examiner has never refuted Appellants' clinical data nor provided evidence that the specifically claimed vaccines will not correlate when administered to humans.

⁵⁴ The Federal Circuit has ruled that in the context of utility, an applicant need not provide a rigorous correlation between *in vitro* and *in vivo* efficacy. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739, 747 (Fed. Cir. 1985) (holding that so long as there is a "reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity . . . [then] a rigorous correlation is not necessary where the disclosure of pharmacological activity is *reasonable* based upon probative evidence") (emphasis added). In *Cross*, the Board had determined that, based upon expert testimony, a showing of "successful *in vitro* testing for a particular pharmacological activity establishes a significant probability that *in vivo* testing for this particular pharmaceutical activity will be successful." *Id.* That same reasonableness standard should apply here where the Examiner's advisory action is based on the alleged lack of correlation between *in vitro* and animal model efficacy data and efficacy in humans. Appellants have surpassed the *Cross* requirement by providing actual *in vivo* animal data.

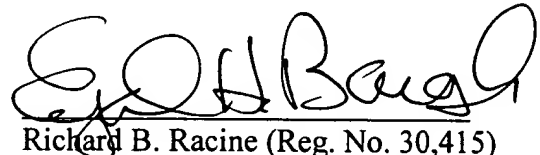
⁵⁵ Exhibit 12, page 6.

By comparison, Appellants have presented data and evidentiary declarations proving the efficacy of the vaccine in the macaque/SHIV model. Moreover, the current thinking in the HIV-vaccine community supports the correlation between the macaque/SHIV model and humans. Under any reasonable standard, therefore, the Appellants have more than met their burden for establishing efficacy and correlation.

XI. CONCLUSION

The Appellants' claimed vaccines protected over 80% of vaccinated macaques, a correlative animal model, from infection of chimeric SHIV, and the evidence submitted to the Examiner explains how and why the macaque is now considered one of the best animal models available for studying HIV therapies in humans. Thus, the Appellants have properly traversed the rejection under 35 U.S.C. § 112, ¶ 1, and the claims should be allowed.

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APPENDIX

Claims — S.N. 08/909,879

19. A vaccine composition comprising:
 - (a) Human Immunodeficiency Virus (HIV) antigen;
 - (b) QS21; and
 - (c) 3-De-O-acylated monophosphoryl lipid A (3D-MPL).
20. A vaccine as claimed in claim 19 wherein the ratio of QS21:3D-MPL is from 1:10 to 10:1.
23. A vaccine composition as claimed in claim 20 wherein the ratio of QS21:3D-MPL is from 1:1 to 1:2.5.
24. A process of making a vaccine composition according to claim 19 comprising admixing QS21 and 3D-MPL with the HIV antigen.